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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,903	01/14/2004	Stephen J. Gunstream	5277 11	4761

22896 7590 01/15/2008

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EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	**PAPER NUMBER**
1797	

MAIL DATE	DELIVERY MODE
01/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,903	GUNSTREAM ET AL.	
	Examiner	Art Unit	
	Arlen Soderquist	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *23-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-22-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Applicant's election without traverse of Group I in the reply filed on October 16, 2007 is acknowledged.

2. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

3. The attempt to incorporate subject matter into this application by reference to all documents cited in the application is ineffective because only US patents and patent publications can be incorporated by reference as noted above.

4. The disclosure is objected to because of the following informalities: the status of the parent/priority applications in paragraph [001] needs to be updated.

Appropriate correction is required.

5. Applicant is advised that should claims 9-11 be found allowable, claims 20-22 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stabile (US 5,854,684) or Ramm (US 6,441,973) in view of Harrison and Glass (US 5,861,256).

In the patent Stabile teaches apparatus for detecting light from closely spaced detection sites. In one embodiment, the invention provides an apparatus for measuring the amount of light emitted from a first set of two or more detection sites, preferably detection wells containing a liquid sample, on a planar substrate/plate while spatially resolving the measurements from each first set detection site. The apparatus includes a source of light directed towards the planar substrate at a first angle; one or more lenses for focusing light emitted or reflected from each of the first set detection sites and having a second angle having an angle offset from the first angle, onto a unique area of an array detector; and the array detector comprising a plurality of light responsive pixels, wherein for each first detection site there is at least one light responsive pixel that receives light emitted or reflected from that detection site and substantially no cross-talk from another detection site, and wherein substantially none of the light from the light source intersects with the array detector. Preferably, the apparatus is designed for use where the emitted or reflected light has a different wavelength than light from the source of light and the apparatus further comprises a filter interposed between the detection sites and the array detector, which filter selectively absorbs the light from the light beam source and transmits light emitted or reflected from the detection sites. Figure 2 shows an embodiment in which two selectable filters are used to select both the excitation frequency and the emission frequency of the light. Preferably, the source light is collimated to increase the accuracy with which the optics minimize cross-talk between detection sites. In one preferred embodiment, the source of light comprises a beam expander, such as a lens, for expanding the cross-sectional area of the light. Preferably, the apparatus further comprises an electrical storage device comprising the plurality of storage registers coupled to the array detector for storing the data from the array detector. Preferably, the apparatus is designed for use with the planar substrate wherein the material between each detection site of the substrate is a blocking material that is opaque or non-reflective to the light from the light source such that substantially no light having the second angle emanates

therefrom. Preferably, the detector array has sufficient light responsive pixels and is designed to work with a planar substrate having sufficient separation between the detection sites so that: (a) there are first light responsive pixels of the detector array that are aligned to receive light emitted or reflected from the first set detection sites; and (b) there are second light responsive pixels of the detector array that receive substantially no light because they are aligned with an area of blocking material, such that for each first set detection site there is a grouping of one or more first light responsive pixels receiving light therefrom and this grouping is separated from the grouping for any other first set detection site by at least one second light responsive pixel. Preferably, at least about twenty-five light responsive pixels are aligned to receive light from each first set detection site such as a charge coupled device (CCD), an intensified CCD array, a focal plane array, a photodiode array or photodetector array. Preferably, the light source is one or more lasers, diode lasers, light emission diodes or superluminescent diodes. The apparatus is designed to detect light emitted or reflected from, or transmitted through, at least about 100 detection sites of the first set and has at least one light responsive pixel aligned with each detection site of the first set. The apparatus is suitable for use in colorimetric, fluorescence, chemiluminescence, fluorescence polarization, time-resolved fluorescence, fluorescence correlation spectroscopy or confocal fluorescence. The apparatus further comprises a processor having access to the stored data; and a motor for moving the substrate, light source or array detector under the control of the processor, wherein the processor is programmed to use one or more initial illuminations of the substrate with the source light to generate data which the processor uses to operate the motor to correct the alignment of the light source, first set detection sites and array detector. Preferably, the processor is programmed to illuminate a first calibration plate having uniform content at its detection sites, which content emits light in response to the illumination, and to collect the data generated by the illumination to diagnose irregularities in the amount of light directed to each detection site and to establish normalization parameters for correcting experimental values for the irregularities in illumination. Preferably, the processor is programmed to illuminate a second calibration plate having uniform content at its detection sites, which content emits substantially no light in response to the illumination, and to collect the data generated by the illumination to calculate the amount of detected light emission that is not due to

the experimental content at the detection sites. If the experimental protocols used with the planar substrates produce detection site contents that are individually sufficiently homogeneous, then calibration procedures and software can be used to normalize for the effects of cross-talk. Stabile does not teach the types of assays measured in the samples or that location dependent biases would be present in the system.

In the patent Ramm teaches an electronic imaging system for assessing the intensity of colorimetric, fluorescent or luminescent signal in a matrix consisting of wells, microwells, hybridization dot blots on membranes, gels, or other specimens. The system includes a very sensitive area CCD detector, a fast, telecentric lens with epi-illumination, a reflective/transmissive illumination system, an illumination wavelength selection device, and a light-tight chamber. A computer and image analysis software is used to control the hardware, correct and calibrate the images, and detect and quantify targets within the images. Relative to wells or microwells, plastic plates are fabricated to contain a number of regularly spaced wells. Standard well plates contain 96 or 384 wells. Very high density arrays of small wells (microwells, e.g. thousands/plate with a fill volume of less than 1 μl/well) are under development, and will become commercially available as microwell filling and detection technologies mature. Column 3, lines 46-65 teach that area imaging systems offer some very attractive potential advantages: the entire specimen is imaged at once, so the detection process can be very quick; with an appropriate illumination system, any excitation wavelength can be applied; and free or fixed format specimens can be imaged. Column 4, line 49 to column 5, line 24 list several advantages of the described system including: selection of illumination wavelengths does not depend on the peak(s) of a gas discharge lamp or laser; a computer-controlled filter wheel or other device allows illumination to be altered during an assay; small alterations in fluorescence emission can be detected due to use of epi-illumination, or from a dorsal or lateral source; and the very efficient camera and unique telecentric lens system allow and entire plate having dim specimens to be imaged without parallax error so well plate assays are accurate. The filter wheel can contain a number of filters, which can be rapidly changed under computer direction. Column 18 teaches that control of an area imaging system is a much more difficult task. Imaging a well plate might include the following requirements: provide

adequate illumination over the entire plate; control a high performance camera; store geometric and density correction factors; image the specimen; correct geometric and density variation; if necessary, calibrate image to standards within the specimen; locate each well and quantify intensity; and transfer data to spreadsheet. The flow chart of figure 9 and its associated discussion describe the process in more detail. Ramm does not teach the types of assays measured in the samples or that location dependent biases would be present in the system.

In the paper Harrison discusses location dependent biases in automatic 96-well microplate readers. Procedures performed in 96-well microplates and quantitated by automatic readers assume instruments to be precise, accurate, and free of well location dependent bias. Instrument specifications generally focus on precision and accuracy without specifically addressing biases which are dependent on well location. These biases appear to be meniscus dependent and can be demonstrated in varying degrees in automatic readers of many designs by using a reverse plate wet test, which compares repeated readings of a dye loaded plate in normal and reversed positions. This test analyzes differences between readings and is, therefore, independent of pipetting error or other experimental variables such as protein binding or immunoassay variability. Different plates increased or decreased the magnitude of observed errors but did not themselves cause the errors measured by the reverse plate wet test. Error patterns were consistent for each reader and varied widely among the 16 instruments tested. Only 4 of 16 instruments passed an existing manufacturer's specification for precision, and only one of the 16 readers tested passed a similar specification for accuracy. The severest location dependent bias was found in an instrument which exhibited excellent repeatability and consistently passed its built-in diagnosis tests. One reader with significant bias was returned to the manufacturer for routine service and calibration, but it was not demonstrably improved. The reverse plate wet test is an extremely useful diagnostic tool for quality control at all stages of instrument manufacture and use.

In the patent Glass provides methods and apparatus for rapidly, accurately, and conveniently detecting and discriminating multiple analytes within a test sample in a clinical laboratory. In particular, the patent provides methods and apparatus for permitting multiple PCR-amplified target nucleic acid sequence hybrids within a single sample, labeled with

different fluorescent dyes, to be spectrally distinguished using the read-out data directly from a fluorescence reader instrument. Accurate detection of biological analytes present in various types of test samples is useful for many purposes including clinical, experimental, and epidemiological analyses. The development of the polymerase chain reaction (PCR) process for amplifying one or more targeted nucleic acid sequences within a sample or mixture of nucleic acid(s) has greatly facilitated processes for detecting and discriminating specific nucleic acid sequences. One problem with PCR is that the process for preparing sample materials for the amplification of nucleic acid sequences are generally difficult and tedious. Generally, the sample must be suitably prepared and then divided into multiple portions such that separate PCR amplification procedures may be performed with different primers, for the different potential target nucleic acid sequences. There are many circumstances wherein it would be useful to simultaneously detect and discriminate between multiple target nucleic acid sequences present or potentially present within a test sample. For example, an accurate diagnosis of an infectious disease may require determining which, if any, of numerous possible infectious agents are present in a clinical sample. In view of the foregoing, it would be advantageous to provide methods and apparatus for improving the efficiency and decreasing the time required to prepare and amplify multiple target nucleic acid sequences within a test sample by permitting various types of sample material to be prepared for non-preferential DNA amplification without laborious nucleic acid extraction and purification steps. It will thus be appreciated that it would be a significant advantage to be able to simultaneously process multiple distinguishably labeled analytes within a single sample such that the multiple analytes can be rapidly, accurately, and conveniently detected and discriminated. Fluorescence-based technology provides multiple potentially distinguishable label moieties. In particular, fluorescent dyes are known which have differing emission and excitation spectra. In theory, the different spectra should be readily distinguishable. Table 1 shows the characteristics of oligonucleotides used in the examples. Table 3 shows the three sequences used in example 1 with their associated dye. Column 10, lines 4-14 teach that for fluorescence detection, 100 ml of PBS, pH 7.4, was added to each well and the plate was read directly on the FL500 Microplate Fluorescence Reader (Bio-Tek Instruments, Inc., Laguna Hills, Calif.). The filter combination (center wavelength in

nanometers/bandwidth in nanometers) and sensitivity settings for each dye were as follows: Bodipy, excitation 485/20, emission 530/25, sensitivity 60; Cy5, excitation 590/20. emission 645/40, sensitivity 80; Tamera, excitation 530/25, emission 590/35, sensitivity 60. The data was recorded as relative fluorescent units ("RFU"). Table 4 shows the 6 sequences used in example 2 with their associated dye. Tables 5-9 show tests to determine optimal settings to distinguish between the six dyes. Column 14, lines 45-59 summarizes the optimal settings that were determined.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate step into the calibration process of Stabile or Ramm to account for any location dependent bias that Harrison teaches as being present because as taught by Harrison the bias can be present even though the instrument shows good repeatability and/or passes internal or manufacturer diagnostic and calibration tests. It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the apparatus or Stabile or Ramm for assays such as the PCR taught by Glass and include calibration steps for each filter setting used because of the need to calibrate for the whole image when multiple dyes are present and need to be distinguished as taught by Glass.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art relates to automated fluorescence plate readers/imagers, calibration of such and different types of assays that can be performed/detected with the plate readers.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (571) 272-1265. The examiner can normally be reached on Monday-Thursday and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Arlen Soderquist
Primary Examiner
Art Unit 1797